UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,103	04/08/2004	Doug Levinson	TPIP038	8971

27777 7590 04/19/2006

PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/821,103	LEVINSON, DOUG	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *20-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☒ Claim(s) *1-4,6-8,10,12 and 15-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. It is noted that claim 23 recites a pharmaceutical composition "according to claim 1". However, claim 1 is directed to a method and not to a pharmaceutical composition. For the purposes of examination claim 23 was assumed to depend from claim 20.

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-19, drawn to a method of producing a composition comprising a protein antigen, classified in class 435, subclass 7.1.

II. Claims 20-30, drawn to a pharmaceutical composition comprising a conformational variant, classified in class 424, subclass 1.41.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the pharmaceutical composition of Group II may be made by a method other than that of Group I, for example, by recombinant expression of a conformationally homogeneous sample comprising a protein antigen that has been previously characterized as having an epitope recognized by a neutralizing antibody.

These inventions are distinct for the reasons given above, have acquired a separate status in the art because of their recognized divergent subject matter and as shown by their different classification. Moreover, the searches required for one group are not required for the others. In

addition to the classification-based search of the patent literature, text searches of the non-patent literature would also be non-coextensive due to the different limitations recited in each group. Therefore, restriction for examination purposes as indicated is proper.

During a telephone conversation with Paul Burgess on December 14, 2005 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-19. Affirmation of this election must be made by applicant in replying to this Office action. Claims 20-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

3. Applicant's Information Disclosure Statement (IDS) filed 3/10/06 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

Claim Objections

4. Claims 1-4, 6-8, 10, 12, and 15-19 are objected to because of the following informalities:

5. The word "comprises" in claim 4 should appear as "comprise" for subject-verb agreement.

6. Part b) of claim 1 is a run-on sentence (...production of neutralizing antibodies, against a pathogen...). It would seem that the clause "against a pathogen..." refers to "neutralizing antibodies", in which case the terms should not be separated by a comma.

7. The preamble of claim 1 refers to a "protein antigen" but the body of the claim refers to a "protein". It is suggested that consistent terminology be employed.

8. The comma in claim 2 is superfluous.

9. The word "structure" should be pluralized in claim 2.

10. Claim 3 refers to clustering "samples", which appears to refer back to the "plurality of samples" recited in claim 1. If Applicant indeed intends to refer back to the samples recited in claim 1, it is suggested that claim 3 refer to "said plurality of samples" or "the plurality of samples" in order to clearly convey this.

11. Claim 4 recites "said criteria comprises", which should read --said criteria comprise--.

12. Claim 4 recites that said criteria comprise "the ability to bind or the affinity for an antibody...". It is unclear from the grammatical structure of the sentence whether "the ability to bind" refers to the ability to bind in general (i.e., the ability to bind anything), or only to the ability to bind to the species listed in the claim (an antibody, to an antigen binding fragment thereof, or a plurality of antibodies). It is also unclear whether the limitation "specific for said protein" recited at the end of the claim is intended to apply only to the "plurality of antibodies" that precedes this, or also to the antibody and antigen binding fragment thereof that are recited earlier in the claim.

13. Claim 6 recites that the conformational variants of claim 1 are obtained by treating "a sample" of protein. However, claim 1 refers to a "plurality of samples".

14. For clarity, it is suggested that part b) of claim 7 recite "binds to one of more neutralizing antibodies with a higher relative binding affinity than **to** one or more non-neutralizing antibodies".

15. In claim 7, the word "affinity" appears to have been inadvertently omitted in part e) between the words "higher" and "than".

16. Claim 8 appears to require an article such as "a" in line 1 between the words "using" and "method".

17. Claim 10 appears to require an article such as "a" in line 1 between the words "wherein" and "covalent linker".

18. Claim 12 has no space between the words "claim" and "1".

19. In claim 15, it appears that the terms "isothermal titration calorimetry" and "equilibrium dialysis" should be separated by a comma.

20. In claim 15 "surface plasma resonance" should read --surface **plasmon** resonance--.

21. Claims 16-19 are objected to for recitation of "**A** method according to claim...", while earlier claims recite "**The** method...". It is suggested that the claims refer to "**The** method according to claim...".

22. Claim 18 appears to require an article such as "a" between "comprises" and "biodegradable".

23. Claim 19 refers to "the protein antigen" in part (i). However, claim 1 refers to a "protein antigen" only in the preamble of the claim, while the body of the claim refers to a plurality of samples comprising a "protein". It is suggested that consistent terminology be employed throughout the claim(s).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. If a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a

sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli* 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of making a vaccine composition comprising a protein that is capable of stimulating the production of neutralizing antibodies against a pathogen from which the protein was derived. The specification defines a "neutralizing antibody" as one that decreases the infectious titre of a preparation of the invading microorganism (p. 6, lines 1-3). Neutralizing antibodies are also defined by the specification as being antibodies that inhibit or block an infectious or pathologic agent at some point in its pathologic process (p. 17, the last paragraph). The specification further indicates that the compositions are vaccine compositions, i.e. that they are capable of decreasing the infectious titre of a microorganism *in vivo* (see in particular p. 6; p. 33, last paragraph to p. 34, the second paragraph). The claimed compositions may comprise any target protein (p. 11, the second paragraph). The claims encompass compositions capable of decreasing the infectious titre of or inhibiting or blocking HIV, anthrax, botulism, enterotoxin, SARS, influenza, measles, ebola, and other infectious or pathologic agents (p. 11, the second paragraph).

The claims are therefore drawn to a method of making a genus of compositions capable of inhibiting or blocking various pathogens--i.e., a genus of *vaccine* compositions. The specification indicates that the claimed compositions comprise a "conformational variant" of the protein. The specification discloses that such conformational variants can be made by denaturing

the protein (see in particular p. 12, the third paragraph) or by cross-linking the protein with a chemical cross-linking agent (see the paragraph bridging p. 13-14).

Although the claims encompass a genus of conformational variant compositions, the specification indicates that a "conformational variant" indicates that the protein differs with respect to the conformation of the native protein. While the members of this genus are all protein antigens, there is no written description of a partial structure or other identifying characteristic that is shared by the members of the genus. Furthermore, the claims encompass proteins derived from a large number of pathogens. Although the members of the genus may be said to share the property of being conformational variants, this property does not serve to identify the claimed genus since it only distinguishes the conformation each member of the genus *from its respective native conformation*. There is no written description that the conformational variants themselves share a common structure. Although it is disclosed that the conformational variants are capable of eliciting neutralizing antibodies, there is no disclosed correlation between this property and any particular structure or identifying characteristic. The specification lacks a description of any identifying structural features shared by the "conformational variant" protein samples and therefore fails to adequately describe the genus.

The claimed method is drawn to identifying protein samples which act as vaccines against a pathogen, yet there is no written description of any such protein samples. The specification does not disclose any specific structures of conformational variants capable of stimulating the production of neutralizing antibodies that were produced according to the claimed method. For example, there is no written description of identifying characteristics of

protein samples that were identified that were capable of eliciting neutralizing antibodies (e.g., the protein's sequence, conformation, etc.).

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

26. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a composition comprising a conformational variant of a protein antigen, does not reasonably provide enablement for a method of producing such a composition that is capable of stimulating the production of neutralizing antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is drawn to a method of producing and/or stabilizing proteins that differ in conformation with respect to a normal or native conformation of the protein. The specification discloses that such conformational variants can be made by denaturing the protein (see in particular p. 12, the third paragraph) or by cross-linking the protein with a chemical cross-linking agent (see the paragraph bridging p. 13-14).

The claims are drawn to a method of making a composition comprising a conformational variant of a pathogen-derived protein, where the conformational variant is capable of stimulating the production of neutralizing antibodies against the pathogen from which the protein was derived. The specification defines a "neutralizing antibody" as one that decreases the infectious

titre of a preparation of the invading microorganism (p. 6, lines 1-3). This definition encompasses decreasing infectious titre both *in vitro* as well as *in vivo* in an infected patient. Further, this definition would include a neutralizing antibody that completely decreases (i.e., eliminates) the infectious titre of a microorganism. Neutralizing antibodies are elsewhere defined in the specification as those that inhibit or block an infectious or pathologic agent at some point in its pathologic process (p. 17, the last paragraph). Again, this would include antibodies capable of completely inhibiting or blocking the infectious or pathologic agent, and at any point in the pathologic process. The specification further indicates that the compositions are vaccine compositions, i.e. that they are capable of decreasing the infectious titre of a microorganism *in vivo* (see in particular p. 6; p. 33, last paragraph to p. 34, the second paragraph). The definition above also encompasses neutralizing antibodies capable of inhibiting or blocking after infection, such that a method of making compositions that may be administered to infected individuals (such as to augment immune response to a virus) would also be encompassed as well as a method of making vaccine-type compositions.

Thus, the claims are drawn to methods of making compositions capable of inhibiting or blocking various pathogens--i.e., a genus of compositions including *vaccine* compositions as well as compositions for treatment that would be capable of inhibiting or blocking pathogens in patients already infected. The claims broadly encompass compositions that may comprise any target protein (p. 11, the second paragraph). The claims also encompass compositions capable of decreasing the infectious titre of or inhibiting or blocking HIV, anthrax, botulism, enterotoxin, SARS, influenza, measles, ebola, and other infectious or pathologic agents (p. 11, the second paragraph).

The specification discloses in Example 1 the preparation of conformational variants of bovine pancreatic trypsin inhibitor (BPTI), which were formed by treating the protein in variable amounts of a denaturant (guanidine hydrochloride). This protein was also treated with a combination of denaturant and cross-linking reagents (p. 41). However, there are no working examples in the specification in which such conformational variant compositions were shown to be capable of stimulating production of neutralizing antibodies against a pathogen (either *in vitro* or *in vivo*). The protein BPTI is a bovine protein, and is therefore not derived from a pathogen, such that the BPTI compositions disclosed in the working example would not be capable of eliciting neutralizing antibodies. With regard to the invention currently being claimed, there are no working examples in which vaccine compositions or compositions capable of stimulating production of neutralizing antibodies against a pathogen were produced.

The prior art teaches that determining whether a composition is capable of stimulating neutralizing antibody production must be determined empirically by screening elicited antibodies to see if they have neutralizing activity (Berman et al, US 6,331,404, column 8, lines 23-39). Thus, it cannot be predicted whether a given composition is capable of stimulating neutralizing antibody production; rather, this must be assessed empirically for each composition. In order to carry out the claimed invention, the skilled artisan would therefore need to produce compositions, raise antibodies against the compositions, and screen the antibodies in order to determine whether the antibodies raised are neutralizing antibodies. However, the prior art teaches that producing antibodies of a determined reactivity is unpredictable (see Paul et al., US 4,468,346, at column 2, lines 19-22; Hung et al., US 5,591,823 at column 3, lines 7-16). The claims encompass compositions comprising proteins that are "derived from" pathogens. Kokolus

et al. (US 5,807,978) teaches that antibodies raised from oligopeptides derived from native proteins do not predictably recognize the native proteins (column 2, lines 1-31).

The prior art further teaches that to date, no vaccine has been effective in conferring protection against HIV infection (see Berman et al., p. 2, lines 37-38). The post-filing literature establishes that an effective HIV vaccine capable of eliciting neutralizing antibodies is not yet in hand (Spearman et al., "Current progress in the development of HIV vaccines", Curr Pharm Des. 2006;12(9):1147-67, the abstract in particular). It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

The prior art teaches that in the case of HIV, which is one of the pathogens disclosed in the instant specification, vaccination with HIV proteins has to date failed to elicit protective immune responses in man (see Gelder et al., US 6,670,181 at column 1, line 60 to column 2, line 14). This is of relevance because the claims recite that the compositions produced are capable of stimulating neutralizing antibodies that can reduce pathogen titer. Gelder et al. further teach that even when neutralizing antibodies are produced, such antibodies have not succeeded in altering

the progression of HIV infection. Wei et al. ("Antibody neutralization and escape by HIV-1" *Nature* Vol. 422, p. 307-312, 2003) similarly teach that neutralizing antibodies are produced by patients that are acutely infected with HIV; however, although such antibodies neutralize virus *in vitro*, they fail to do so *in vivo* (see the abstract and the paragraph bridging p. 311-312). This is of relevance because the claims encompass vaccine compositions capable of inhibiting or blocking HIV both *in vitro* and *in vivo*, yet the prior art teachings above indicates that even when neutralizing antibodies are produced, they may not be capable of inhibiting or blocking HIV *in vivo*.

In order to produce the claimed compositions, the specification directs the skilled artisan to identify conformational variants capable of stimulating the production of neutralizing antibodies can be identified by identifying samples that are capable of binding to (previously known) neutralizing antibodies or that bind with higher affinity to neutralizing antibodies than to non-neutralizing antibodies (see for example p. 18-19). In particular, the specification teaches that protein antigens that bind to a neutralizing antibody may elicit the production of antibodies which recognize the same epitope; such antibodies would be expected to possess neutralizing activity (see the paragraph bridging p. 19-20). However, the prior art teaches that protein antigens may bind to neutralizing antibodies but may not be capable of inhibiting infectivity (see Berman et al. above at column 47, lines 28-43, which teaches that "high antibody binding alone is not sufficient for neutralization"). In this light, the specification fails to provide the skilled artisan with sufficient direction/guidance in producing the claimed compositions, since compositions identified by their ability to bind to neutralizing antibodies would not necessarily be capable of inhibiting infectivity.

Furthermore, the prior art teaches unpredictability with respect to interactions between pathogens and host immune system. In the case of HIV, Yang et al. ("Genetic and Stochastic Influences on the Interaction of Human Immunodeficiency Virus Type 1 and Cytotoxic T Lymphocytes in Identical Twins" *Journal of Virology* 2005, Vol. 79, No. 24, p. 15368-15375) teach that stochastic influences render the interaction of HIV-1 with the host immune system unpredictable (see the abstract and p. 15373-15374). The teachings of Wei et al. (discussed above) in which it was shown that antibodies capable of neutralizing HIV-1 *in vitro* were not capable of blocking the virus *in vivo*, also reflect the unpredictability associated with production of neutralizing antibodies. Moreover, as discussed above, determining whether a composition is capable of stimulating neutralizing antibody production cannot be predicted but must be determined empirically by screening elicited antibodies to see if they have neutralizing activity (Berman et al, column 8, lines 23-39).

In summary, the prior art teaches that protein compositions capable of binding to neutralizing antibodies do not necessarily inhibit pathologic agents, and further, that even those compositions that are capable of eliciting neutralizing antibodies do not necessarily inhibit or block pathologic agent activity *in vivo*. Furthermore, the prior art also teaches unpredictability in the interaction of HIV-1 with the host immune system as well as unpredictability in producing neutralizing antibodies that are effective in inhibiting or blocking pathogens *in vivo*. The specification lacks direction/guidance regarding identifying conformational variants capable of stimulating the production of neutralizing antibodies, since it has been shown that proteins that bind to neutralizing antibodies do not necessarily inhibit infectivity. Finally, in light of the lack of working examples showing production of a conformational variant composition that is capable

of stimulating the production of neutralizing antibodies, and in light of the breadth of the claims, which encompass methods of producing vaccine compositions against any type of pathogen, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without undue experimentation.

27. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the production of a composition comprising a protein antigen. The claim concludes with the step of "identifying" a sample comprising a conformational variant of a protein in part b). However, the claim lacks a step in which a composition comprising a protein antigen is produced, as recited in the preamble of the claim.

29. Claim 1 recites the limitation "the conformation state" in part a). There is insufficient antecedent basis for this limitation in the claims.

30. Claim 1 recites that the protein was "derived" from a pathogen in part b). The specification does not define the term "derived" and does not set forth processes by which proteins are derived from pathogens. The use of this terminology does not allow for the metes and bounds of the claim to be adequately determined.

31. Claim 1 recites neutralizing antibodies "against a pathogen", which is vague and indefinite. The term "against a pathogen" does not clearly describe how the antibodies and the pathogen are related.

32. Claim 2 recites the limitation "said conformational variants". Similarly, claims 6-7, 9, 17, and 19 refer to "said conformational variants" as well as to "said conformational variant" and "the conformational variant". There is insufficient antecedent basis for these limitations in the claims. Claim 1 refers to a sample that comprises a conformational variant, but not to a conformational variant or variants *per se*.

33. Claim 3 recites the "step of clustering samples" based on "a profile of selected criteria". The claim is vague and indefinite because it is unclear in what sense the samples are clustered—i.e., are the protein samples physically sorted or pooled in groups, or are they being classified or categorized as the result of an analysis (i.e., a mental step)? In addition, the recitation of a "profile of selected criteria" is vague. The use of this terminology does not allow for the metes and bounds of the claim to be adequately determined.

34. Claim 5 recites the limitation "said antibody". There is insufficient antecedent basis for this limitation in the claims. Claim 5 depends from claim 4, which refers to "an antibody" as well as a "plurality of antibodies". Claim 1 refers to "neutralizing antibodies". It is unclear what "said antibody" is referring to.

35. Claim 5 recites conditions a) through e). The claim is indefinite because it is unclear whether the claim requires that the antibody fulfill any one of the conditions or all of them since the list of conditions are not separated by "or" or "and".

36. Claim 5 recites that the antibody is contacted with the protein in the presence of biological fluids. The claim is indefinite because the relationship of this step to the claimed method of producing a composition is unclear. Is the contacting step performed in order to identify the sample comprising a conformational variant as in part b) of claim 1? Or is this a

separate, additional method step? It is unclear how this contacting step relates to the method objective of producing a composition comprising a protein antigen.

37. Similarly, in claim 7, it is unclear whether conditions a) through h) are all intended to be limitations or whether they are intended to be recited in the alternative.

38. Similarly, in claim 19, it is unclear whether conditions (a) through (l) are all intended to be limitations or whether they are intended to be recited in the alternative.

39. Claim 6 recites "treating a sample of protein having a native conformation under different conditions" in part (b). It is unclear from the sentence structure whether the sample is treated under different conditions, or alternatively, whether the protein has a native conformation under different conditions.

40. Claim 7 recites the limitation "the native conformation" in parts e), g), and h). There is insufficient antecedent basis for this limitation in the claims.

41. Claim 7 recites the limitation "the increase in affinity of f)" in part g). There is insufficient antecedent basis for this limitation in the claims.

42. Claim 8 recites that the protein is structurally characterized using the methods of "hydrophobic interaction" and "affinity". The claim is indefinite because it is unclear what methods "hydrophobic interaction" and "affinity" are intended to encompass since these terms do not refer to techniques.

43. Claim 5 recites that the antibody is contacted with a protein in the presence of biological fluids. It is unclear whether this refers to an actual method step that is performed during the method.

44. Claim 8 recites that the protein is "structurally characterized" using one of the recited methods. It is unclear whether the structural characterization constitutes an active method step, or merely indicates, for example, that the protein has been previously structurally characterized. It is noted that should the claim(s) be rewritten to recite additional process steps they may be subject to further restriction.

45. Similarly, in claim 9, it is unclear whether the stabilization using a covalent linker is an active step performed during the method, or rather indicates that a covalent linker was already attached to the protein sample provided in step a) of claim 1.

46. Similarly, claim 12 recites that a purification step enriches a sample for a conformational variant. It is unclear whether such a purification step is actually performed during the method.

47. Similarly, claims 13-14 recite that the sample(s) are enriched. It is unclear whether such an enrichment is an active method step that is performed during the method, or whether the sample(s) were previously enriched.

48. Claim 12 recites that a sample is enriched using "ion exchange, chromatography". It is unclear whether Applicant intends to recite "ion exchange chromatography" or "ion exchange chromatography" as well as "chromatography". For the purposes of examination the reference was assumed to refer to "ion exchange chromatography".

49. Similarly, claim 15 recites that affinity is measured by one of the recited techniques. It is unclear whether the techniques are actually performed during the claimed method.

50. Similarly, claim 16 recites "a sample comprising a conformational variant or subset" in lines 2-3. It is unclear whether the sample is the same one that is referred to in part b) of claim 1.

51. Claim 8 recites "intrinsic" and "extrinsic" fluorescent probes. The terms are indefinite because they are not defined in the specification.

52. Claim 11 recites the limitation "said linker target", for which there is insufficient antecedent basis. Claim 9 refers to a "covalent linker" and not to a "linker target".

53. Claim 11 recites the limitation "the amino acid sequence", for which there is insufficient antecedent basis.

54. Claim 12 refers to "a sample" that is enriched for "a conformational variant". It is unclear whether the sample is the same sample that comprises a conformational variant referred to in part b) claim 1, or alternatively whether a distinct sample and a distinct conformational variant are being recited.

55. Claim 13 recites the limitation "said sample", while claim 14 recites "said samples". There is insufficient antecedent basis for these limitations in the claims since claim 1 refers both to a plurality of samples and to a sample that comprises a conformational variant. It is unclear which of these sample(s) is being referred to in claims 13-14.

56. Claim 16 recites the limitation "each conformational variant sample". There is insufficient antecedent basis for this limitation in the claims as claim 1 only refers to "a" sample that comprises a conformational variant.

57. Claim 17 recites that the conformational variant "is bound to a microparticle". The claim is indefinite because it is unclear whether the conformational variant is already bound to a microparticle in the sample provided in part a) of claim 1, or whether this refers to a subsequent method step in which the conformational variant sample identified in part b) of claim 1 is reacted with a microparticle.

58. Claim 19 is rejected as indefinite for improper wording of a Markush-type group in part (l). It is suggested that the claim recite an immunostimulatory molecule **selected from the group consisting of** the recited species, as in parts (c)-(f) of the claim.

59. Claim 19 recites the limitations "the microparticle core" and "the surface of the microparticle" in parts (b) and (i). There is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 102

60. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

61. Claims 1-10, 12-13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Lang et al. ("Monoclonal Antibodies that Define Neutralizing Epitopes of Pertussis Toxin: Conformational Dependence and Epitope Mapping" *Infection and Immunity,* 1989, Vol. 57, p. 2660-2665) and in light of Kiernan ("Formaldehyde, formalin, paraformaldehyde and glutaraldehyde: What they are and what they do" *Microscopy Today* **00-1** p. 8-12 (2000), obtained from http://publish.uwo.ca/~jkiernan/formglut.htm on 4/10/06).

Lang et al. teach a method of producing a composition comprising a protein antigen (pertussis toxin, PT), comprising providing a plurality of samples comprising PT that differ with respect to the conformation state of the protein. For example, purified native PT, detoxified PT treated with formalin, and isolated PT subunits were used as samples to immunize mice (see the

abstract and p. 2660; p. 2661, "Cytotoxicity assay" and Table 1; p. 2661, right column, "Results and Discussion to p. 2662, left column, second paragraph). Lang et al. further teach that native PT, detoxified PT, and some of the isolated subunit samples were capable of stimulating the production of antibodies that neutralized the cytotoxicity of PT (Table 1 and above-mentioned passages).

With respect to claim 2, the native and detoxified PT have the same primary amino acid sequence but differ with respect to secondary/tertiary structure in that detoxified PT is cross-linked (p. 2662, left column, the first full paragraph). The samples also differed in secondary/tertiary structure since Lang et al. teach that the neutralizing antibodies recognized conformation-dependent antigenic determinants (p. 2664, second paragraph).

With respect to claims 3-5, Lang et al. teach the step of clustering the antigen samples based on the ability to bind to the elicited neutralizing antibodies (Table 1 and p. 2661, right column, "Results and Discussion to p. 2662, left column, second paragraph). The antibodies are contacted with the proteins in the presence of "biological" since the binding reactions occur in fluid samples that are being used in a biological assay.

With respect to claim 6, the native PT protein was treated under different conditions to produce the formalin-detoxified PT sample (i.e., with or without formalin). Lang et al. also teach that formalin cross-linking may stabilize the PT molecule (p. 2662, left column, the first full paragraph). Lang et al. also teach that PT had "a native conformation" under different conditions in that the S1 subunit retained the ability to bind to anti-PT polyclonal antibody (and therefore a native conformation) in the immunoblot assay, in which detergent was present (p. 2661, right column, "Results and Discussion").

With respect to claim 7, Lang et al. identified samples that that bound to the neutralizing antibodies elicited (Table 1) and that stimulated the production of neutralizing antibodies *in vivo* in mice.

With respect to claim 8, PT was structurally characterized by affinity chromatography (p. 260, "Purification of PT" and by enzymatic activity (p. 2661, "NAD glycohydrolase assay).

With respect to claims 9-10, the Kiernan et al. reference is relied upon as an evidentiary reference for its teaching that formalin, which was reacted with PT by Lang et al., is a covalent linker in that it forms covalent cross-links or methylene bridges between protein atoms (Kiernan et al., p. 2-3, "Reaction of formaldehyde with proteins"). Kiernan et al. further evidences that formalin targets amino groups such as those on lysine residues of proteins (ibid and Figure 2).

With respect to claims 12-13, Lang et al. teach purification of PT samples by affinity chromatography and ion exchange chromatography on a CM-sepharose CL-6B column (p. 2660-2661, "Materials and Methods").

With respect to claim 15, Lang et al. teach measurement of the binding affinity using ELISA (immunoblot analysis employing enzyme-linked antibody conjugates) (see p. 2661, "SDS-PAGE and immunoblots").

62. Claims 1, 3-8, 12-13, and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Berman et al. (US 6,331,404 B1).

Berman et al. teach a method of producing a compositions comprising a protein antigen (HIV envelope proteins such as gp120) that are capable of stimulating the production of neutralizing antibodies against HIV (the abstract and column 3, lines 5-37). Berman et al. teach

providing a plurality of gp120 samples (gp120 fragments, mutagenized gp120 fragments, and/or gp120 proteins isolated from different HIV strains (column 6, lines 43-51; column 9, lines 3-39; column 11, lines 60-67). These samples differ with respect to the conformation state because they have different amino acid sequences.

With respect to claims 3-5 and 15, Berman et al. further teach clustering the samples based on their binding to various monoclonal antibodies (column 40, lines 23-59; column 41, line 17 to column 44, line 60, and Tables 4-5). The binding is assessed by ELISA. The monoclonal antibodies tested included both neutralizing and non-neutralizing antibodies (Table 4). The antibodies are contacted with the proteins in the presence of "biological" since the binding reactions occur in fluid samples that are being used in a biological assay.

With respect to claim 6, Berman et al. teach that the secondary or tertiary structure of the gp120 fragments are stabilized in that the neutralizing antibody epitopes are preserved. Berman et al. also teach that the fragments may have the same glycosylation and disulfide bonds as native gp120 (column 9, lines 14-23).

With respect to claim 7, Berman et al. teach that the gp120 fragments bind to neutralizing antibodies (Tables 4-5). Berman et al. teach that some samples bound to neutralizing antibodies with higher relative affinity than to one or more non-neutralizing antibodies (see Table 5, compare the binding of the sample MN-rgp120 to neutralizing antibodies 1024, 1093, 1096, 1097, 1100, 1112, 1127 to the binding to the non-neutralizing antibody 5C2; see also column 43, lines 22-27). Berman et al. further teach that the samples were capable of stimulating the production of neutralizing antibodies *in vivo* as vaccine compositions (column 11, line 60 to column 12, line 67; column 49, line 60 to column 50, line 27). Berman et al. further teach that

some of the samples bound to neutralizing antibodies with higher affinity than the antibodies bound to the native or non-mutant form of gp120 (MN-rgp120); see Table 5, where the numbers represent binding relative to binding of MN-rgp120. The difference in affinity of a neutralizing antibody for native vs. mutant form is greater than the difference in affinity of the non-neutralizing antibody for native vs. mutant forms in some instances. For example, Berman et al. compare the binding of neutralizing antibody 1096 in Table 5 to native (MN-rpg120) and the conformational variant MN-421A. The difference in affinity is 1.6-1.0, or 0.6. For the non-neutralizing antibody 5C2, the difference in affinity of binding for MN-423F vs. MN-rgp120 is 0.4.

With respect to claims 8 and 12-13, Berman et al. teach that the gp120 may be subjected to immunoaffinity and ion exchange chromatography (column 49, lines 52-60).

With respect to claim 16, Berman et al. teach contacting the gp120 samples with both neutralizing (antibodies 1024, 1093, 1096, 1097, 1110, 1112, and 1127) and non-neutralizing antibodies (5C2) (Table 5). The MN-rpg120 binds to the neutralizing antibodies with higher affinity than to the non-neutralizing antibody.

Claim Rejections - 35 USC § 103

63. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

64. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lang et al. in light of Kiernan as applied to claim 9 above, and in view of Densham et al. (US 6,623,929).

Lang et al. is as discussed above, which teaches pertussis toxin samples treated with the covalent crosslinking reagent formalin, but which fails to specifically teach that the linker target is created by *in vitro* mutagenesis.

Densham et al. teach strategies for crosslinking proteins, in which site-directed mutagenesis may be employed to introduce reactive groups into proteins in order to allow them to react with crosslinking reagents (column 4, lines 25-39).

Therefore, it would have been obvious to one of ordinary skill in the art to employ site-directed mutagenesis as taught by Densham et al. to modify the pertussis toxin of Lang et al. in order to ensure reactivity with crosslinking reagents.

65. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lang et al. in light of Kiernan as applied to claim 12 above, and in view of Rasmussen et al. (US 4,743,562).

Lang et al. is as discussed above, which teaches methods of enriching and purifying samples of pertussis toxin by affinity chromatography and ion exchange chromatography, but which fails to specifically teach that the samples are enriched using neutralizing antibodies.

Rasmussen et al. teach that neutralizing antibodies raised from a purified protein may be used for isolating the protein by affinity chromatography by coupling the monoclonal forms of the antibodies to a solid support (see in particular the abstract and column 3, line 35 to column 4, line 30).

Therefore, it would have been obvious to one of ordinary skill in the art to use the neutralizing antibodies raised by Lang et al. in order to isolate pertussis toxin samples by affinity chromatography. One would have a reasonable expectation of success because affinity chromatography is one method taught by Lang et al. for purifying pertussis toxin.

66. Claims 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berman et al. or, alternatively, Lang et al. in light of Kiernan, in view of O'Hagan et al. (US 6,458,370).

Berman et al. and Lang et al. are as discussed above, which teach compositions comprising conformational variants of gp120 and pertussis toxin, respectively, that are capable of eliciting neutralizing antibodies, but which fail to specifically teach that the conformational variants are bound to a microparticle having a diameter of up to 150 microns.

O'Hagan et al. teach biodegradable microparticles having adsorbed or entrapped antigens, which may be used in methods of immunization (the abstract; column 3, lines 38-41; column 4, lines 34-67). The microparticles may be made of biodegradable polymers such as poly(alpha-hydroxy acid), polyhydroxybutyric acid, polyanhydridepoly(D,L-lactide-co-glycolide) or other materials, and have diameters up to about 150 microns (see also column 9, lines 22-44). O'Hagan et al. teach that combination of antigens with such microparticles enhance the immunogenicity of the antigen (column 3, lines 29-37), which includes the ability of the antigen to elicit an antibody-mediated immune response (column 5, lines 51-65). Proteins to be adsorbed to the surface of the microparticles (or entrapped within) include HIV gp120 (column 8, lines 19-53). The microparticles may further comprise immunostimulating agents (column 12, lines 4-13).

Therefore, it would have been obvious to one of ordinary skill in the art to bind the compositions of Berman et al. or Lang et al. to the microparticles of O'Hagan et al. because O'Hagan et al. teaches that including microparticles enhances the immunogenicity of protein antigens. One would have a reasonable expectation of success because O'Hagan et al. teach that the microparticles can be combined proteins intended to elicit antibody responses, which is the purpose of the compositions of Berman et al. and Lang et al. One would also have a reasonable expectation of success in combining the teachings of O'Hagan et al. with those of Berman et al. since O'Hagan et al. specifically teach the protein antigen gp120, which is the protein used by Berman et al.

Conclusion

67. No claims are allowed.

68. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Haigwood et al. (US 5,614,612) is cited for its teaching of recombinant HIV gp120 proteins as vaccine compositions. Haigwood et al. is also of relevance to claim 13 for its teaching of various methods of purifying gp120 antigens including ion exchange chromatography, hydrophobic interaction chromatography, and gel filtration chromatography (column 3, lines 20-30 in particular).

Fischinger et al. (US 6,290,963 B1) teach HIV gp120 compositions of both native and deglycosylated forms of gp120 (column 3, lines 13-67) that are capable of stimulating the production of neutralizing antibodies against HIV (Examples 1-3).

Locht (US 5,786,189) is cited for its teaching of microparticles comprising aluminum hydroxide as an adjuvant for use in vaccine compositions.

Houghten et al. (US 2002/0002272) also teach aluminum hydroxide as an adjuvant as well as the use of immunostimulatory molecules such as IL-4, IL-5, and IL-6 in immunogenic compositions (paragraph 86).

Day et al. (US 6,821,519) also teach inclusion of cytokines such as IL-4, IL-6, and IL-6 that induce humoral immune responses in vaccine compositions (column 59, line 63 to column 4, line 12) as well as aluminum hydroxide and aluminum salts as adjuvants in such compositions (column 59, lines 44-62). Day et al. also teach linking agents for coupling peptides to carrier proteins; the peptides can include a cysteine residue for conjugation to the carrier protein (see in particular column 8, lines 17-50).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

cfoster

Christine Foster, Ph.D.
Patent Examiner
Art Unit 1641

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
04/14/06